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Kocher-Debré-Sémélaigne syndrome diagnosed by autopsy associated with disseminated intravascular coagulation

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Abstract Kocher-Debré-Sémélaigne syndrome is a rare disease with little literature, which develops with myopathy in infancy associated with neuromuscular alterations, polymyositis with symmetrical proximal muscle weakness, pseudohypertrophy, muscular rigidity and spasms, exercise intolerance, myxoedema, short stature, and cretinism. Male patient aged 18 years old, 1.52 m in height, admitted in the General Hospital of Triângulo Mineiro Federal University on November 11, 2003, complaining of intense diffuse abdominal pain like severe cramps, without triggering factors, associated with asthenia and hyporexia. This seems to be one of the few reports of KDS syndrome diagnoses by autopsy, where alterations in the thyroid gland connected with hypotrophy and probable congenital hypothyroidism were described and resulted in complications such as

Keywords: Disseminated intravascular coagulation; Kocher-Debré-Sémélaigne; Hemophagocytic syndrome

1. Introduction

The deficiency of the thyroid hormone is responsible for 5% of the cases of acquired myopathies, and its association with muscle pseudohypertrophy is called Kocher-Debré-Sémélaigne syndrome (KDS) [1]. KDS syndrome is a rare disease with little literature, which develops with myopathy in infancy associated with neuromuscular alterations, polymyositis with symmetrical proximal muscle weakness, pseudohypertrophy, muscular rigidity and spasms, exercise intolerance, myxoedema, short stature, and cretinism [2]. Neuromuscular symptoms are present in 30% to 80% of the patients with hypothyroidism [3] and may improve or reduce in accordance with the functional condition of the thyroid gland and the use of hormone replacement therapy [2,3].

Kocher-Debré-Sémélaigne syndrome predisposes to a weakness of the defense system, which contributes to the establishment of infections, making them more serious and of difficult control, and these infections may culminate in the onset of sepsis [2,4,5]. On the other hand, sepsis is an important cause of disseminated intravascular coagulation (DIC), a serious clinical condition whose mortality is connected with the control of the triggering mechanism, such as fungal or bacterial infections and posttransfusion reactions [6,7].

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Therefore, this report aims at presenting a KDS syndrome case that, after infection and sepsis, developed DIC and hemophagocytic syndrome resulting in the death of an 18-year-old patient with the final diagnosis established only during the autopsy.

2. Case report

A male patient aged 18 years old, 1.52 m in height, admitted in the General Hospital of Triângulo Mineiro Federal University on November 11, 2003, complaining of intense diffuse abdominal pain like severe cramps, without triggering factors, associated with asthenia and hyporexia. He had been presenting not assessed spiking fevers, sudoresis, and chills since the previous day, evolving into little responsive state of torpor related to jaundice and choluria. As personal history of morbidity, he had presented febrile seizures from the age of 6 months until 11 years, cognitive deficit, and growth alterations. At 11 years, his hand and wrist x-rays revealed bone age of 8 years, with the weight-height evolution less than 2.5 for height and less than 10 for weight. At his physical examination, he was tachydyspneic, was afebrile (37,1°C), presented pale mucous membranes, was dehydrated and jaundiced, had intercostal retraction, had diffuse pulmonary rales, had petechiae in the chest, had hepatosplenomegaly, and had Glasgow Coma Scale score of 7, with no meningeal irritation signs. He had syndromic face, low set ears, short neck, hypodevelopment, bilateral syndactyly of the feet, palmar simian line, and grade 1 cardiomegaly. Antibiotic therapy was started at hospital admission. There was a worsening of the tachypnea, and the patient was submitted to orotracheal intubation with mechanical ventilation, and a red blood cell concentrate transfusion was conducted. The examination results showed the following alterations: severe anemia, with 1.72 erythrocytes × 10^6/mm^3, 5.4 g of hemoglobin, 16% of hematocrit; thrombocytopenia, platelet counts 33.000 × 10^3/mm^3; increased prothrombin time (PT) and activated partial thromboplastin time (APTT) (PT: International Normalized Ratio [INR], 2.3; APTT: *R*[Patient APTT/mean normal APTT] = 1.34); leukocytosis with discreet left shift; fasting glucose test, 116 mg/dL; aspartate aminotransferase, 565 U/L, alanine aminotransferase, 482 U/L, lactate dehydrogenase, 2650 U/L; creatine phosphokinase, (CPK), 4795 U/L; urea, 112 mg/dL; and creatinine, 2.4 mg/dL.

On November 12, 2003, the patient presented a spiking fever of 38.8°C, and megaloblastic anemia was detected by myelography. On November 14, there was an onset of bloody vomits, bradycardia, and undetectable blood pressure, progressing to cardiopulmonary arrest and death.

3. Anatopathologic examination

A probable congenital hypothyroidism characterized by prominent hypotrophy of the thyroid with reduction in the number and size of this gland was diagnosed (observed weight, 2 g; expected weight, 15-20 g; Fig. 1A). There were multiple malformations such as macroglossia, micrognathia, slanting of the palpebral fissures, short neck, increase of subcutaneous tissue, short lower and upper limbs, small hands with short fingers, enlargement of the space between the first and second finger, bilateral syndactyly between the third and fourth toes, and generalized muscle hypertrophy. A systemic infection was characterized during the autopsy, represented by encephalitis, moderate bilateral interstitial pneumonitis, chronic esophagitis, chronic tracheobronchitis, and moderate chronic enteritis (Fig. 1B, C). The disseminated intravascular coagulation was characterized by disseminated microthrombi, mainly in small vessels in the kidneys, vocal cords, lung, spleen, pancreas, liver, lymph nodes, intestine, adrenal, and heart (Fig. 1D, E). There was gingival and conjunctival hemorrhage in the true vocal cords and in the places of venipuncture, with blood extravasation into the subcutaneous tissue. Petechiae diffusely distributed over skin, and serous membranes were observed, mainly on the pleura and pericardium. Moderate hemophagocytosis was noticed in the spleen, lymph nodes, and bone marrow, according to the diagnosis of hemophagocytic syndrome. Moreover, the patient presented heart failure with anasarca featured by generalized subcutaneous edema, mainly in lower limbs, accentuated hydrothorax, ascites and pericardial effusion, marked splenic congestion, severe palpebral edema with exophthalmia, and inversion of the lower eyelid, as well as cardiac liver with a moderate periportal and diffuse mononuclear infiltrate. A moderate hypertrophy of the left ventricle, cardiac vessels with reactive endothelium and occlusive hyaline thrombi, and also diffuse hemorrhagic spots were also observed.

4. Discussion

This report describes a clinical picture of an 18-year-old patient with hemophagocytic syndrome, DIC, and systemic infection, associated with congenital hypotrophy of the thyroid and probable KDS syndrome diagnosed by autopsy.

Results of laboratory tests to confirm hypothyroidism and KDS syndrome were not found in the clinical history. Most of the reports about this syndrome is based on laboratory findings [5,8]. During autopsy, the hypotrophy of the thyroid follicles and low weight of the gland were associated with probable congenital hypothyroidism, which, in 80% of the cases, is related to agenesis, ectopia, and hypoplasia of the thyroid gland [9].

Another factor that contributed to the hypothesis of congenital hypothyroidism was the clinical diagnosis of megaloblastic anemia. Studies demonstrate that there is a high prevalence, approximately 40%, of vitamin B_{12} deficiency in patients with hypothyroidism [10].

The probability of hypothyroidism in this case was also increased by the great number of external malformations and

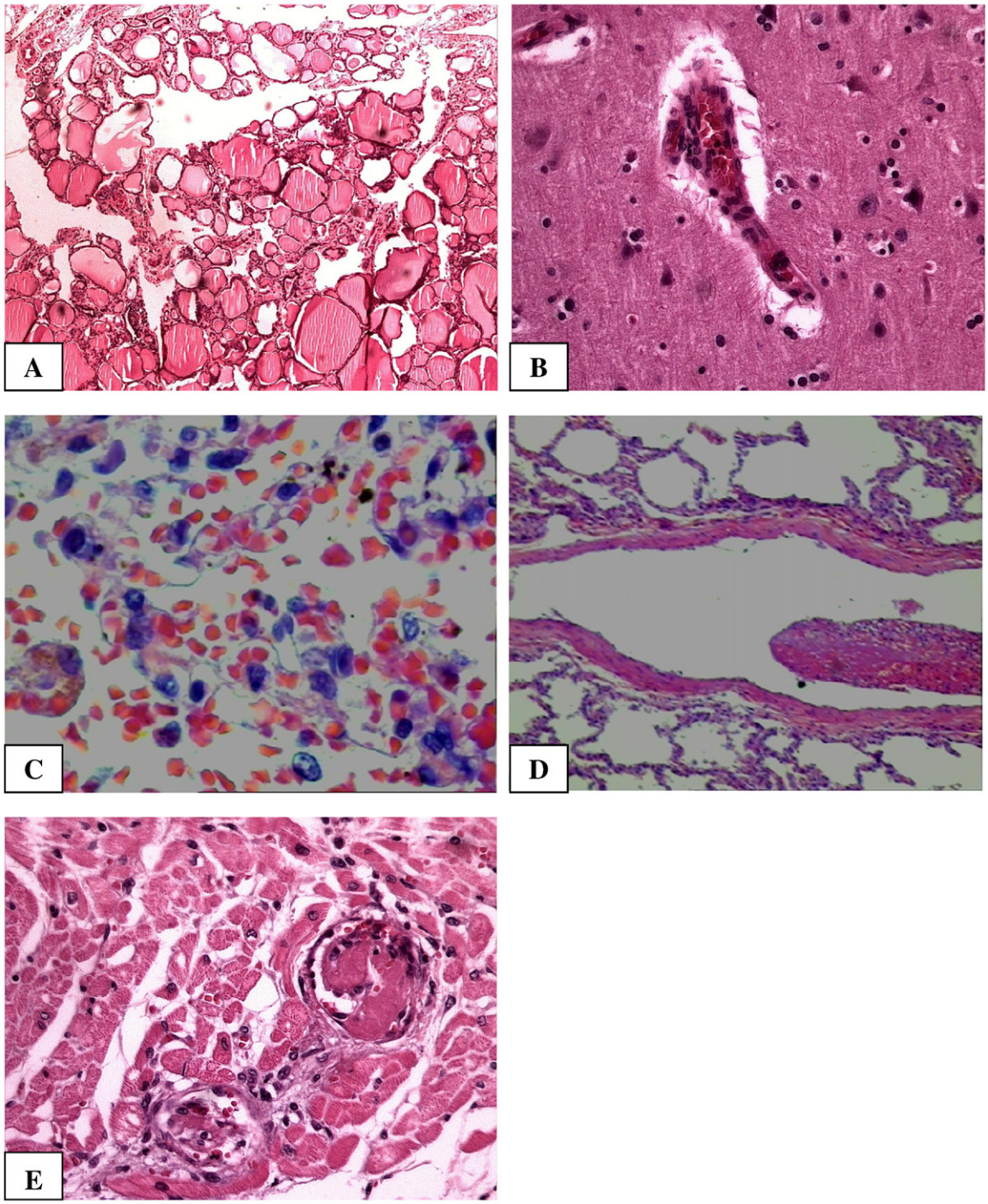

Fig. 1. (A) Hypotrophy of the thyroid characterized by reduced number and size of the thyroid follicles, 50×. A systemic infection represented by encephalitis, with inflammatory infiltrate in the vessels and edema (×250) (B), and moderate bilateral interstitial pneumonitis (250×) (C). The disseminated intravascular coagulation characterized by disseminated microthrombi in small vessels in the lung (250×) (D) and heart (250×) (E).

the delay in mental and corporal development observed [11]. Thyroid hormone deficiency is frequently connected with delay in bone development, low stature, and mechanical failure of the growth plates of the hips (slipped capital femoral epiphyses) [12]. In animal models of hypothyroidism, the deficiency of T3 results in delay in the skeleton ossification and also in important alterations in the growth plates, such as thickness reduction, disorganization of the cartilage, and impediment of the differentiation of proliferative chondrocytes into hypertrophic chondrocytes [13]. This patient's low stature (1.52 m) compared with what is expected for his age reinforces our findings. Moreover, a greater frequency of extrathyroid congenital malformations is reported in children with hypothyroidism, which is another

argument to support the role of a genetic component in the etiology of congenital hypothyroidism [11], and that, in this case, may be related to the multiple malformations observed.

At least 79% of patients with hypothyroidism have symptoms of muscle weakness, cramps, and myalgia. Nonspecific muscle rigidity may be associated with increased serum muscle enzyme, as serum CPK [14]. One of the findings of the KDS syndrome is pseudohypertrophy, observed in about 10% of the patients with hypothyroidism [2,15] and characterized in this autopsy as generalized muscle hypertrophy. Pseudohypertrophy involves the extremity muscles, trunk, hands, and feet and is more evident in limbs. Its pathogenesis has not been established yet and may be present in several types of hypothyroidism [1].

An important component of the KDS syndrome is myopathy, which in this case may be connected with the complaints of asthenia and the increase of CPK levels, often altered under stress, and lesion in the skeletal musculature, as well as aspartate aminotransferase and alanine aminotransferase, which may change during the course of hypothyroidism [1]. The thyroid hormone acts in nearly all aspects of the metabolism. In hypothyroidism, there is a decrease of the metabolic function and of the protein turnover, which compromises many organs or systems, including the muscular system [2,15,16]. This decrease is connected with the hypertrophic muscle aspect, having both been observed in this patient.

The onset of the KDS syndrome is often between the ages of 18 months and 10 years; however, there are reports of findings in the perinatal period. These data accord with the conditions observed in this report that show the existence of the syndrome symptoms, such as cognitive deficit and growth alterations from the age of 6 months. However, the KDS syndrome development in this case may be related to the absence of hypothyroidism diagnosis and, consequently, to the other alterations related to it, because the hypothesis of the syndrome was only proposed in the course of the autopsy.

Kocher-Debré-Sémélaigne syndrome progresses with muscular, metabolic, and neurologic alterations, predisposing to poor immune response and making the individual susceptible to infections and, in more severe cases, to sepsis [2,5]. On the other hand, sepsis is an important cause of DIC [15], a serious clinical condition whose mortality is associated with the control of the triggering mechanism. In this study, we observed a decrease in vascular resistance, leukocytosis with a marked left shift, alterations in the renal function and blood coagulation characterized by petechiae and thrombocytopenia, DIC, increase of the APTT, and hyperglycemia in the absence of diabetes. These findings are in accordance with the signs of sepsis, where the decrease in systemic vascular resistance, the increase of the cardiac output, and laboratorial alterations are evident, as described in this study [4].

Endocrine alterations such as hypothyroidism are among the most frequent causes of macrophage activation syndrome, a condition that progresses with temperature and hepatosplenomegaly and presents high case fatality rates and diagnostic difficulty [5]. In this case, the macrophage activation syndrome was secondary to an infection, probably viral, characterized by encephalitis, moderate bilateral interstitial pneumonitis, chronic esophagitis, chronic tracheobronchitis, and moderate chronic enteritis. The endocrinologic alteration may have favored the onset of an extremely severe infection that developed into sepsis, DIC, hemophagocytic syndrome, multiple system failure, and death of the patient.

This seems to be one of the few reports of KDS syndrome diagnoses by autopsy, where alterations in the thyroid gland connected with hypotrophy and probable congenital hypothyroidism were described and resulted in complications such as DIC and hemophagocytic syndrome with fast progression to death of an 18-year-old patient.

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